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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,758	LIANG ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-12,14-25,27-41 and 43-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-12, 14-25, 27-41 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed March 19, 2004. Claims 1-3, 5-12, 14-25, 27-41 and 43-46 were previously pending. Applicants amended claims 1, 10, 21, 30, 38 and 44. Claims 1-3, 5-12, 14-25, 27-41 and 43-46 are pending and will be examined.

2. Applicants' amendments overcame the following: objection to specification over introduction of new matter into specification; rejection of claims 10, 11, 14 and 16 under 35 U.S.C. 102(a) as anticipated by Cassata et al.; rejection of claims 1, 2, 5, 6, 10, 12, 14, 15, 21, 22, 27-29, 30-34 and 46 under 35 U.S.C. 102(b) as anticipated by Shi et al.; rejection of claims 3, 20, 23 and 35 under 35 U.S.C. 103(a) over Shi et al. and Felgner et al.; rejection of claims 7, 8, 17, 18, 24, 25, 36 and 37 under 35 U.S.C. 103(a) over Shi et al. and Uhlman et al.; rejection of claims 7, 9, 17 and 19 under 35 U.S.C. 103(a) over Shi et al. and Goodchild; rejection of claims 38-41 and 43 under 35 U.S.C. 103(a) over Shi et al. and Mullis et al.; rejection of claims 44 and 45 under 35 U.S.C. 103(a) over Shi et al. and Uhlman et al. All other rejections are maintained for reasons given in the "Response to Arguments" section below.

3. Applicants' amendments introduced new grounds for rejection which are presented below.

Response to Arguments

4. Applicant's arguments filed March 19, 2004 have been fully considered but they are not persuasive.

Regarding the rejection of claims 9, 19, 25, 37 and 45 under 35 U.S.C. 112, first paragraph, written description, Applicants argue that an amendment to the specification presented in the response filed March 19, 2004 provides basis for these claims. However, this is not the case. In the original specification Applicants incorporated by reference U.S. Patent No. 5,459,127, which describes cationic lipids. In the current amendment Applicants cite a part of this patent which

describes modified nucleotides. In the original specification, however, Applicants did not cite parts of the 5,459,127 patent which were to be relied on. Further, the subject matter of the 5,459,127 patent has nothing to do with amplification of a target sequence, as it deals with delivery of nucleic acids to cells in cationic liposomes. As stated in MPEP 608.1(p) IA:

MPEP 608.01(p)

I. INCORPORATION BY REFERENCE

A. Review of Applications Which Are To Issue as Patents.

> "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by **35 U.S.C. 112**, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found."

Therefore, the amendment to the specification constitutes new matter and does not provide support for claims 9, 19, 25, 37 and 45.

The rejection is maintained.

Specification

5. The amendment filed March 19, 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the paragraph added to the paragraph starting on page 8, line 26.

Applicant is required to cancel the new matter in the reply to this Office Action. In the original specification Applicants incorporated by reference U.S. Patent No. 5,459,127, which describes cationic lipids. In the current amendment Applicants used a part of this patent which describes modified nucleotides. In the original specification, however, Applicants did not cite parts of the 5,459,127 patent which were to be relied on. Therefore, addition of this part of the 5,459,127 patent to the specification constitutes a new matter.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 9, 19, 25, 37 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn nuclease resistant moieties being phosphorothioates. There is no basis in the specification for theses claims. The amendment to specification introducing this subject matter is considered to be a new matter (see above), therefore these claims are not supported by the specification.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Before proceeding with the rejections, it is noted that the term "nucleic acid sequence that confers function" is interpreted in its broadest meaning, i.e., any function that can be assigned to a nucleic acid.

10. Claims 1, 2, 5, 6, 10-12, 14-16, 21, 22, 27-34 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993).

Regarding claim 1, Shi et al. teach a method for amplifying a transcriptionally-active polynucleotide, comprising:

performing a first PCR amplification step to amplify a first fragment of DNA with a first primer pair, wherein the first primer pair, upon such amplification, adds to first and second ends of the first fragment predetermined first and second regions of complementarity, to form a second DNA fragment having said first region of complementarity at a first end and a second region of complementarity at a second end of said second DNA fragment (Shi et al. teach synthesis of human Lym-1 antibody gene by PCR from fourteen oligonucleotide fragments (page 46, fifth paragraph; page 47, first paragraph; Fig. 1). The two main fragments contained amplified V_H and V_L regions of the Lym-1 antibody, which were 615 or 522 bp and 422 bp in size, respectively (page 46, fifth paragraph; page 47, third and fourth paragraphs; Fig. 1; page 50, second paragraph). Therefore, the V_H and V_L fragments were the targets for amplification (Fig. 1). In the first step of PCR, the two fragments were contacted with primers 1-9 (page 49, third paragraph; Fig. 1). As can be seen from Fig. 1, primers 7 and 9 add to the V_H fragment first and second regions of complementarity, which are complementary to regions of primers 8 and 10, primers 5 and 8 add to the V_L fragment first and second regions of complementarity, which are complementary to regions of primers 7 and 6, etc. Therefore, at any point during the amplification reaction, each fragment, is contacted sequentially

with two primers, both of which contain regions of complementarity to which the next two primers anneal.);

providing a promoter-containing sequence and a terminator-containing sequence, said promoter-containing sequence further including a region complementary to said first region of complementarity, and said terminator-containing sequence further including a region complementary to said second region of complementarity, wherein both said promoter-containing sequence and said terminator-containing sequence include an internal nucleotide capable of forming an A-T base pair immediately adjacent to said region of complementarity (Shi et al. teach providing fragments containing the hybrid λ phage promoter sequence and terminator sequence (page 49, third paragraph). Both the first fragment and the tenth fragment contain nucleotides capable of forming an A-T base pair immediately adjacent to the regions of complementarity (Table 2; page 51, third paragraph.));

joining said promoter-containing sequence to said first end of said second DNA fragment and said terminator-containing sequence to said second end of said second DNA fragment to form said third DNA fragment (Shi et al. teach PCR amplifying the V_H and V_L fragments with fragments 1-9 which contain the promoter and terminator, therefore joining the promoter and terminator-containing fragments to fragments V_H and V_L (Fig. 1; page 49, third paragraph).); and

performing a second PCR amplification step to amplify said third DNA fragment (Shi et al. teach a second step PCR amplification of the whole gene using primers 2 and 10 (page 49, third paragraph; Fig. 1).).

Regarding claim 2, Shi et al. teach PCR amplifying the V_H and V_L fragments with fragments 1-9 which contain the promoter and terminator, therefore joining the promoter and terminator-containing fragments to fragments V_H and V_L (Fig. 1; page 49, third paragraph).

Regarding claims 5 and 6, Shi et al. teach Vent or Taq polymerase (page 49, fourth paragraph; page 50, first paragraph).

Since claim 21 is broader than claim 10, they will be considered together.

Regarding claims 10 and 21, Shi et al. teach a method of adding a nucleic acid sequence that confers function to a polynucleotide target sequence, the method comprising:

contacting first and second nucleic acid fragments with a polynucleotide target sequence, wherein the first nucleic acid fragment comprises a first region of complementarity to a portion of the polynucleotide target sequence and a first extension region, and the second nucleic acid fragment comprises a second region of complementarity to a portion of the polynucleotide target sequence and a second extension region (Shi et al. teach synthesis of human Lym-1 antibody gene by PCR from fourteen oligonucleotide fragments (page 46, fifth paragraph; page 47, first paragraph; Fig. 1). The two main fragments contained amplified V_H and V_L regions of the Lym-1 antibody, which were 615 or 522 bp and 422 bp in size, respectively (page 46, fifth paragraph; page 47, third and fourth paragraphs; Fig. 1; page 50, second paragraph). Therefore, the V_H and V_L fragments were the targets for amplification (Fig. 1). In the first step of PCR, the two fragments were contacted with primers 1-9 (page 49, third paragraph; Fig. 1). As can be seen from Fig. 1, primers 7 and 9 add to the V_H fragment first and second regions of complementarity, which are complementary to regions of primers 8 and 10, primers 5 and 8 add to the V_L fragment first and second regions of complementarity, which are complementary to regions of primers 7 and 6, etc. Therefore, at any point during the amplification reaction, each fragment, is contacted sequentially with two primers, both of which contain regions of complementarity to which the next two primers anneal.);

performing a first PCR amplification step comprising amplifying the first and second nucleic acid fragments and the polynucleotide target sequence, to form an intermediate nucleic acid fragment that comprises the polynucleotide target sequence flanked by the first and second extension regions (Shi et al. teach a first PCR amplification step using primers 1-9 (page 49, third paragraph; Fig. 1).);

contacting the intermediate nucleic acid fragment with a third and fourth nucleic acid fragments that respectively comprises a region complementary to the first and second extension regions, wherein one or both of the third and fourth nucleic acid fragments further comprise at least one nucleic acid region that confers function (Shi et al. teach PCR amplifying the V_H and V_L fragments with fragments 1-9 which contain the promoter and terminator, therefore joining the promoter and terminator-containing fragments to fragments V_H and V_L (Fig. 1; page 49, third paragraph).); and

performing a second PCR amplification step comprising amplifying the intermediate nucleic acid fragment with the third and fourth nucleic acid fragments to form a product nucleic acid fragment that comprises one or more functional nucleic acid regions joined to the polynucleotide target sequence (Shi et al. teach a second step PCR amplification of the whole gene using primers 2 and 10, generating a nucleic acid containing functional nucleic acid regions (page 49, third paragraph; Fig. 1).).

Regarding claim 11, Shi et al. teach nucleic acid fragments 1-9, which contain regions of complementarity to a target and extension regions, which are not complementary to the target, for example, fragments 1-9 (Fig. 1; page 49, third paragraph).

Regarding claims 12, 22 and 29, Shi et al. teach nucleic acid regions which comprise a promoter and a terminator (page 49, third paragraph).

Regarding claims 14, 15, 27 and 28, Shi et al. teach Vent or Taq polymerase (page 49, fourth paragraph).

Regarding claim 11, Shi et al. teach nucleic acid fragments including an internal nucleotide capable of forming an A-T base pair immediately adjacent to the extension region (Table 2).

Regarding claim 30, Shi et al. teach a reaction mixture (= system for adding a nucleic acid fragment that confers function to a polynucleotide sequence), comprising:

an extension primer pair, each primer of which comprises a region of complementarity to a strand of the polynucleotide target sequence and a predetermined extension region (Shi et al. teach a reaction mixture that contains the oligonucleotides with sequences complementary to the target sequence and extension regions , such as oligonucleotides 1-9 (extension primer pairs) (Fig. 1, page 49, third paragraph); and

a 5' biological function conferring nucleic acid fragment and a 3' biological function conferring nucleic acid fragment, each fragment of which comprises a region of complementarity to one of the extension regions, and a biological function conferring polynucleotide sequence that confers biological function, wherein the extension primer pairs are adapted to add the extension regions to a target sequence upon a first PCR procedure, and the function conferring nucleic acid pairs are adapted to add the functional polynucleotide sequences to the target sequence upon a second PCR procedure (Shi et al. teach a reaction mixture that contains oligonucleotides which contain a promoter and a terminator, respectively (= biological function conferring polynucleotides) (page 49, third paragraph). The limitation following "wherein" is an intended use limitation, therefore they do not impose structural limitation upon the claimed product.).

Regarding claims 31-33, Shi et al. teach a reaction mixture Taq polymerase (page 49, fourth paragraph).

Regarding claim 34, Shi et al. teach a reaction mixture comprising an oligonucleotide which comprises a promoter (page 49, third paragraph).

Regarding claim 46, Shi et al. teach a reaction mixture comprising an oligonucleotide which comprises a terminator (page 49, third paragraph).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 3, 20, 23 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993) and Felgner et al. (U. S. Patent No. 6,165,720; cited in the IDS and in the previous office action).

A) The teachings of Shi et al. are described above. Shi et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach insertion of a PNA-binding domain.

B) Regarding claims 3, 20, 23 and 35, Felgner et al. teach construction of nucleic acid vectors (or plasmids) containing PNA-binding sites (col. 12, lines 46-67; col. 13, lines 1-26; col. 26, lines 64-67; col. 27, 28; Fig. 8). The PNA-binding sites confer the following properties onto the plasmids: increased transfection efficiency, nuclear localization, transcription activation, endosomal lytic activity and immunostimulatory activity (col. 6, lines 29-47).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added PNA-binding sites of Felgner et al. to transcriptionally-active nucleic acids of Shi et al. The motivation to do so, provided by Felgner et al. would have been that binding of

PNA clamps to PNA-binding sites provided nuclease resistance to DNA duplexes (col. 6, lines 48-54).

13. Claims 7, 8, 17, 18, 24, 25, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993) and Uhlman et al. (U. S. Patent No. 6,063,571; cited in the previous office action).

A) The teachings of Shi et al. are described above. Shi et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach PNA molecules which confer nuclease resistance.

C) regarding claims 7, 8, 17, 18, 24, 25, 36 and 37, Uhlman et al. teach amplification of nucleic acids with DNA/PNA primers, which contain a PNA moiety at the 5' end of the primer. Such primers can be used with temperature-stable polymerases (col. 2, lines 30-49; col. 5, lines 8-46). Uhlman et al. teach that nucleic acid fragments amplified with DNA/PNA primers are resistant to exonucleases (col. 1, lines 32-39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the DNA/PNA primers of Uhlman et al. in the amplification method of Shi et al. The motivation to do so, provided by Uhlman et al., would have been that PNA confers nuclease resistance to a DNA attached to it (col. 1, lines 32-39).

14. Claims 7, 9, 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993) and Goodchild (Bioconjugate Chemistry, vol. 1, pp. 165-187, 1990; cited in the previous office action).

A) The teachings of Shi et al. are described above. Shi et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach addition of at least one phosphorothioate during the amplification reaction.

B) Regarding claims 7, 9, 17 and 19, Goodchild teaches oligonucleotides modified with phosphorothioates and nuclease resistance of such oligonucleotides (page 167, the last paragraph, continued on page 168; page 170, paragraphs 3-6; page 175, paragraphs 9-11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used phosphorothioate-modified oligonucleotides of Goodchild as primers in the amplification reaction of Shi et al. The motivation to do so, provided by Goodchild, would have been that phosphorothioates provided nuclease protection to nucleic acids (page 175, paragraphs 12 and 13).

15. Claims 38-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993) and Mullis et al. (U.S. Patent No. 4,965,188; cited in the previous office action).

A) Regarding claim 38, Shi et al. teach a method of adding a nucleic acid sequence that confers function to a polynucleotide target sequence, the method comprising:

contacting first and second nucleic acid fragments with a polynucleotide target sequence, wherein the first nucleic acid fragment comprises a first region of complementarity to a portion of the polynucleotide target sequence and a first extension region, and the second nucleic acid fragment comprises a second region of complementarity to a portion of the polynucleotide target sequence and a second extension region (Shi et al. teach synthesis of human Lym-1 antibody gene by PCR from fourteen oligonucleotide fragments (page 46, fifth paragraph; page 47, first paragraph; Fig. 1). The two main fragments contained amplified V_H and V_L regions of the Lym-1 antibody, which were 615 or 522 bp and 422 bp in size, respectively (page 46, fifth paragraph; page 47, third and fourth paragraphs; Fig. 1; page 50, second paragraph). Therefore, the V_H and V_L fragments were the targets for amplification (Fig. 1). In the first step of PCR, the two fragments were

contacted with primers 1-9 (page 49, third paragraph; Fig. 1). As can be seen from Fig. 1, primers 7 and 9 add to the V_H fragment first and second regions of complementarity, which are complementary to regions of primers 8 and 10, primers 5 and 8 add to the V_L fragment first and second regions of complementarity, which are complementary to regions of primers 7 and 6, etc. Therefore, at any point during the amplification reaction, each fragment, is contacted sequentially with two primers, both of which contain regions of complementarity to which the next two primers anneal.);

performing a first PCR amplification step comprising amplifying the first and second nucleic acid fragments and the polynucleotide target sequence, to form an intermediate nucleic acid fragment that comprises the polynucleotide target sequence flanked by the first and second extension regions (Shi et al. teach PCR amplifying the V_H and V_L target fragments with fragments 1-9, which are equivalent (Fig. 1; page 829, second paragraph).);

contacting the intermediate nucleic acid fragment with a third and fourth nucleic acid fragments that respectively comprises a region complementary to the first and second extension regions, wherein one or both of the third and fourth nucleic acid fragments further comprise at least one nucleic acid region that confers function (Shi et al. teach contacting the intermediate products, for example, products of amplification of the V_H and V_L targets with primers 5, 6, 7, 8 and 9 with fragments 1-4, which contain a promoter (= transcriptionally functional region) (page 49, third paragraph; Fig. 1.)); and

performing a second PCR amplification step comprising amplifying the intermediate nucleic acid fragment with the third and fourth nucleic acid fragments to form a product nucleic acid fragment that comprises one or more functional nucleic acid regions joined to the polynucleotide

target sequence (Shi et al. teach PCR amplifying the gene with fragments 2 and 10, producing a transcriptionaly active product (Fig. 1; page 49, fourth paragraph; Fig. 5).).

Regarding claims 39 and 40, Shi et al. teach a transcriptional functional region being a promoter or a terminator and addition of both to the final gene sequence (page 49, third and fourth paragraph).

Regarding claim 43, Shi et al. teach amplification using a Vent or Taq polymerase (page 49, fourth paragraph).

B) Shi et al. do not teach amplification of more than one target nucleic acid or separate amplification of different targets.

C) Regarding claim 38, Mullis et al. teach that in polymerase chain reaction more than one target nucleic acid can be amplified using primers specific for each target (col. 3, lines 1-67; col. 4, lines 1-5; col. 13, lines 20-30). The primers may have sequences non-complementary to the target attached at the 5' end of the primers, and the non-complementary sequences may contain promoters, linkers, coding sequences, etc. (col. 6, lines 44-53; col. 19, lines 60-67; col. 20, lines 1-6).

Regarding claim 41, Mullis et al. teach amplification of different target nucleic acids in separate tubes (col. 34, lines 57).

It would have been *prima facie* obvious to one of ordinary skill in the art to have amplified more than one target nucleic acid according to Mullis et al. in the method of gene synthesis of Shi et al. The motivation to do so, provided by Mullis et al., was that multiple nucleic acids are produced in large quantities (col. 9, lines 36-41).

16. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993) and Uhlman et al. (U. S. Patent No. 6,063,571; cited in the previous office action).

Regarding claim 44, Shi et al. teach a method of adding a nucleic acid sequence that confers function to a polynucleotide target sequence, the method comprising:

contacting first and second nucleic acid fragments with a polynucleotide target sequence, wherein the first nucleic acid fragment comprises a first region of complementarity to a portion of the polynucleotide target sequence and a first extension region, and the second nucleic acid fragment comprises a second region of complementarity to a portion of the polynucleotide target sequence and a second extension region (Shi et al. teach synthesis of human Lym-1 antibody gene by PCR from fourteen oligonucleotide fragments (page 46, fifth paragraph; page 47, first paragraph; Fig. 1). The two main fragments contained amplified V_H and V_L regions of the Lym-1 antibody, which were 615 or 522 bp and 422 bp in size, respectively (page 46, fifth paragraph; page 47, third and fourth paragraphs; Fig. 1; page 50, second paragraph). Therefore, the V_H and V_L fragments were the targets for amplification (Fig. 1). In the first step of PCR, the two fragments were contacted with primers 1-9 (page 49, third paragraph; Fig. 1). As can be seen from Fig. 1, primers 7 and 9 add to the V_H fragment first and second regions of complementarity, which are complementary to regions of primers 8 and 10, primers 5 and 8 add to the V_L fragment first and second regions of complementarity, which are complementary to regions of primers 7 and 6, etc. Therefore, at any point during the amplification reaction, each fragment, is contacted sequentially with two primers, both of which contain regions of complementarity to which the next two primers anneal.);

performing a first PCR amplification step comprising amplifying the first and second nucleic acid fragments and the polynucleotide target sequence, to form an intermediate nucleic acid fragment that comprises the polynucleotide target sequence flanked by the first and second

extension regions (Shi et al. teach PCR amplifying the V_H and V_L target fragments with fragments 1-9, which are equivalent (Fig. 1; page 829, second paragraph).);

contacting the intermediate nucleic acid fragment with a third and fourth nucleic acid fragments that respectively comprises a region complementary to the first and second extension regions, wherein one or both of the third and fourth nucleic acid fragments further comprise at least one nucleic acid region that confers function (Shi et al. teach contacting the intermediate products, for example, products of amplification of the V_H and V_L targets with primers 5, 6, 7, 8 and 9 with fragments 1-4, which contain a promoter (= transcriptionally functional region) (page 49, third paragraph; Fig. 1.)); and

performing a second PCR amplification step comprising amplifying the intermediate nucleic acid fragment with the third and fourth nucleic acid fragments to form a product nucleic acid fragment that comprises one or more functional nucleic acid regions joined to the polynucleotide target sequence (Shi et al. teach PCR amplifying the gene with fragments 2 and 10, producing a transcriptionaly active product (Fig. 1; page 49, fourth paragraph; Fig. 5).).

B) Shi et al. teach addition of promoter and terminator to a nucleic acid fragment, but do not teach PNA molecules which confer nuclease resistance.

C) Regarding claims 44 and 45, Uhlman et al. teach amplification of nucleic acids with DNA/PNA primers, which contain a PNA moiety at the 5' end of the primer. Such primers can be used with temperature-stable polymerases (col. 2, lines 30-49; col. 5, lines 8-46). Uhlman et al. teach that nucleic acid fragments amplified with DNA/PNA primers are resistant to exonucleases (col. 1, lines 32-39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the DNA/PNA primers of Uhlman et al. in the amplification method of Shi

et al. The motivation to do so, provided by Uhlman et al., would have been that PNA confers nuclease resistance to a DNA attached to it (col. 1, lines 32-39).

17. No claims are allowed.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
October 22, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER